An Analysis of Factors in the Approval of Orphan Drugs for the Rarest Diseases

by

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Abstract

An orphan drug is a pharmaceutical developed for a rare disease. This study analyzed how many orphan drugs were approved relative to the prevalence of these rarer diseases and, additionally, what influences pharmaceutical companies into developing orphan drugs for a limited population. The hypothesis was that the rarest diseases receive the most attention, and, therefore, there are more drugs approved for diseases with the lowest prevalence compared to more prevalent diseases. An analysis of approved orphan drugs for the last thirty years was conducted using a search on the U.S. FDA website and disease prevalence was systematically compiled using the primary source National Organization for Rare Disorders database. The results demonstrate that the prevalence rate of a disease does not correlate with the frequency of approval of an orphan drug for the rarest diseases. However, more research is needed to address motivating factors for developing orphan drugs.

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Introduction

In 1983, the Orphan Drug Act was passed to stimulate drug development for rare diseases. Prior to this legislative passage, pharmaceutical companies had fewer incentives to develop drugs for small populations because of the expectations that they would be unprofitable and require extensive legal measures (United States Department of Health and Human Services, 2001). In order to ensure rare disease treatment, the government has incentivized pharmaceutical companies to develop drugs for rare indications since 1983. Such drugs for rare diseases are referred to as orphan drugs. Government intervention on behalf of orphan drug development can take a variety of forms:

- 7 year marketing exclusivity to sponsors of approved orphan drug products
- Research grants for clinical testing for new orphan therapies
- Tax credit of 50 percent of the cost of human clinical testing (United States Department of Health and Human Services, 2001).

From 1983 to 2014, there have been more than 400 drugs that have been developed for an orphan indication out of the now more than 2000 orphan designations (Food and Drug Administration, 2015, National Organization for Rare Diseases, 2015 and Wellman-Labadie & Zhou, 2010). It is clear that drug development for rare diseases is influenced by government incentives and thus the Orphan Drug Act has been successful (Wellman-Labadie & Zhou, 2010). This paper analyzes the relationship between approved orphan drugs and the prevalence of rare diseases. For purposes of this analysis, if a disease had a population less than or equal to 50,000 people out of the entire population of the United States, it was classified as a rarest disease. Although the Orphan Drug Act includes all diseases with a prevalence below 200,000, this analysis was confined to diseases with a prevalence $\leq$50,000.

In this paper, the hypothesis tested was that the rarest diseases receive the most attention and, therefore, there are more drugs approved for the diseases with a lower prevalence compared to those with a higher prevalence. Pharmaceutical companies may develop orphan drugs out of goodwill for the patients experiencing these rare debilitating or fatal diseases. Additionally, the industry may profit from orphan drug sales. This study was important because of the limited information available on what influences the drug approval for the rarest disease populations.

Research question

1. Do the number of approved orphan drugs correlate with the prevalence of the rarest diseases?
2. What motivates pharmaceutical companies to make orphan drugs for the rarest diseases?

Methods

A systematic analysis of approved orphan drugs in the United States for the last thirty years was conducted using a search on the Food and Drug Administration (FDA) website (2015). Prevalence rate of a disease is defined as the number of people affected as a proportion of the whole population of the United States. Prevalence is defined as the approximate number of people with the disease in the United States. The population of the United States as of the year 2014 was gathered using the DemographicsNow database (2015) and was listed as 317,352,277 people. The prevalence or prevalence rate per disease was gathered using National Organization for Rare Diseases (NORD) (2015). When there were no prevalences given in the NORD database, a calculation was conducted by multiplying the disease prevalence rate with the United States population. A scale from 0 to 50,000, was created and organized into prevalence blocks of 5,000. When considering populations, an assumption was made to focus analysis on the U.S. because the facts collected about orphan drugs are U.S. based.

Search Strategy

The search strategy was carried out using several data sources:

Websites: Food and Drug Administration

Databases: National Organization for Rare Disorders (NORD, 2015), Pubmed, Cinahl

Data Collection

1. A list of 476 orphan drugs was collected from the Food and Drug Administration website that were approved and marketed during the last thirty years (from July 20, 1983-October 31, 2014). These dates range from after the implementation of the Orphan Drug Act in 1983 through when the database was accessed.

2. The National Organization for Rare Disease (NORD) database (a primary source of information on rare diseases) was accessed for information regarding prevalence, incidence rate, or prevalence rate for each rare disease.
3. The number of orphan drugs approved for each rare indication was tabulated.
4. A drug was excluded when it had an indication outside the rare disease category (above 200,000 prevalence population).
5. Drugs with multiple indications were considered only for one disease. If a disease associated with an orphan drug was not listed in the NORD database, that particular disease was excluded from further analysis assuming it is not a rare disease.
6. In calculating the prevalence for each of the rare diseases, the prevalence rate or the incidence rate of each disease was multiplied by the total population of the United States (DemographicsNow, 2015). If a rare disease contained a range of prevalence, then the median value was considered.
7. A graph was created of the number of orphan drugs versus the prevalence in increments of 5,000. Ranges were defined such that a prevalence group included prevalences greater than the lowest value up to those equal to the highest value.

Results

After tabulating the data from the NORD database and the FDA website, there were 96 rare diseases that fit the search criteria (See Appendix A for the list of rare diseases that were considered in this study). For some of these diseases, it was difficult to determine the prevalence from the NORD database due to incomplete data entries. In those situations, some of the data regarding incidence, prevalence or prevalence rate in rare diseases were gathered from a variety of disease-related organization websites. Due to the uncertainty of population demographics, missing prevalence data, and/or if the prevalence rates were higher than 50,000, the list of rare diseases and their associated drugs were decreased from 96 to 53 (See Appendix B for the final list of approved orphan drugs and their related disease). There were 132 approved orphan drugs for 53 rare indications (Table 1). The data were analyzed to evaluate the relationship between the prevalence and the frequency of orphan drug approval for the rarest indications.

Table 1

Approved number of orphan drugs and the corresponding rare disease indication

≤ Prevalence	Approved number of Orphan Drugs	Number of Rare diseases
5,000	56	25
5,000-10,000	21	10
10,000-15,000	9	2
15,000-20,000	9	3
20,000-25,000	1	1
25,000-30,000	7	4
30,000-35,000	4	1
35,000-40,000	1	1
40,000-45,000	8	2
45,000-50,000	16	4
Total	132	53

Figure 1 displays the number of orphan drug approvals by prevalence.

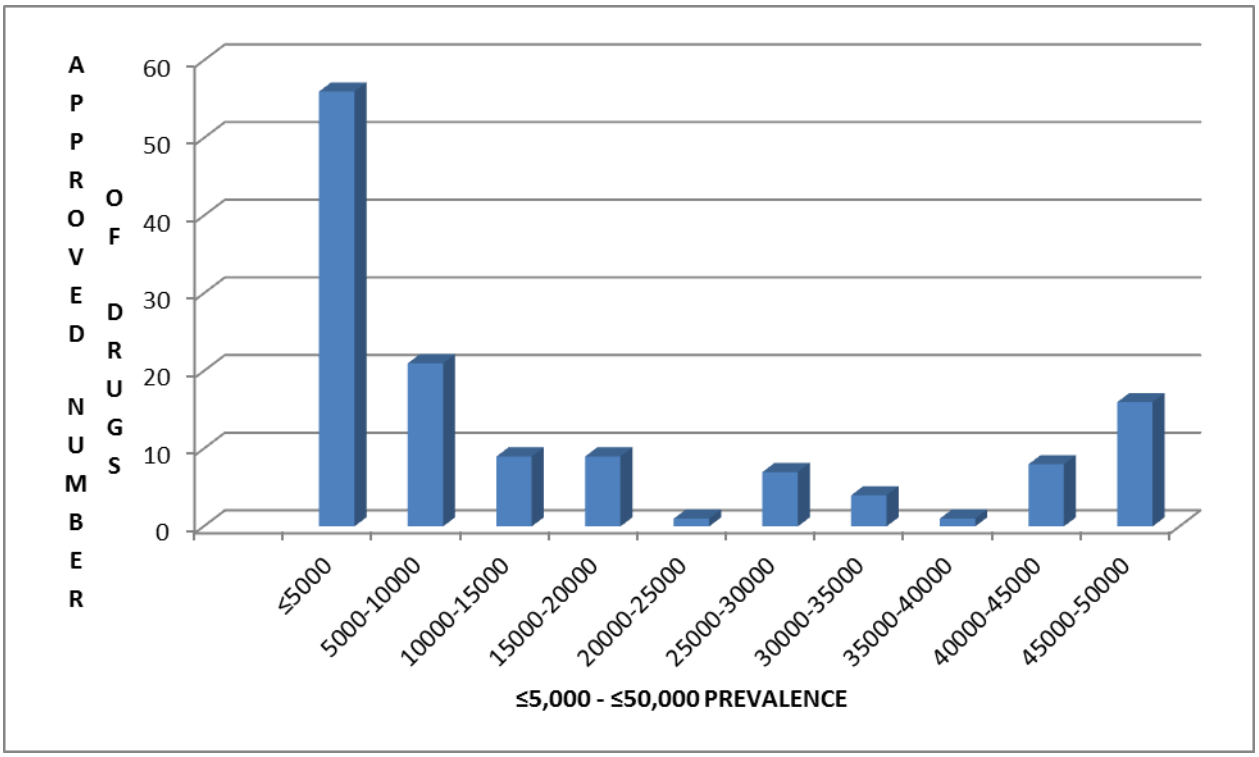

Figure 1: Orphan Drug Approvals by Disease Prevalence. Graph depicts the number of drugs approved for all diseases included in this study within prevalence ranges in increments of 5,000.

Figure 2 displays the number of diseases included in this study for each prevalence group of increments of 5,000.

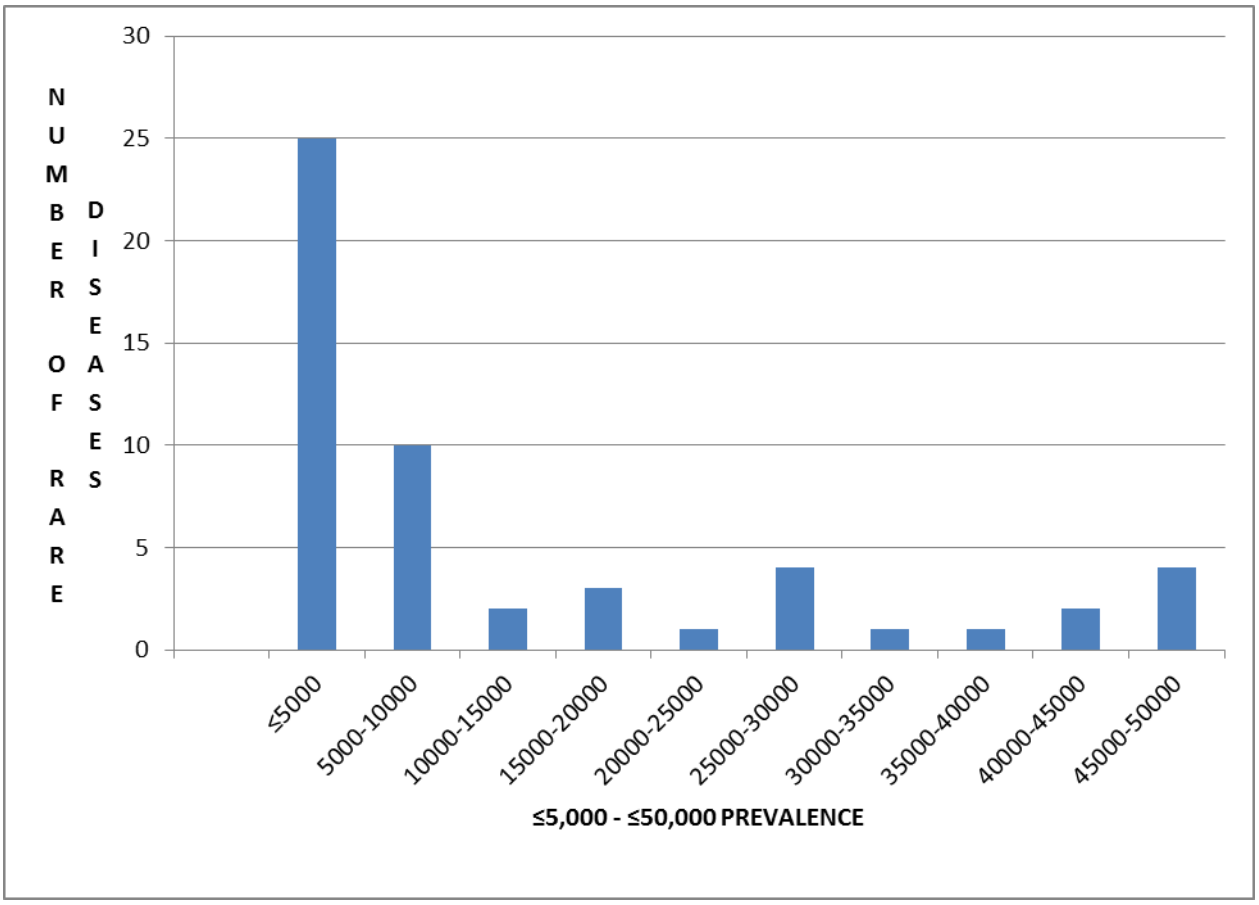

Figure 2: Number of Rare Diseases by Disease Prevalence Group. Graph depicts the number of diseases from this study included within each prevalence range in increments of 5,000.

Figure 3 displays the ratio of approved drugs to number of diseases in that prevalence category.

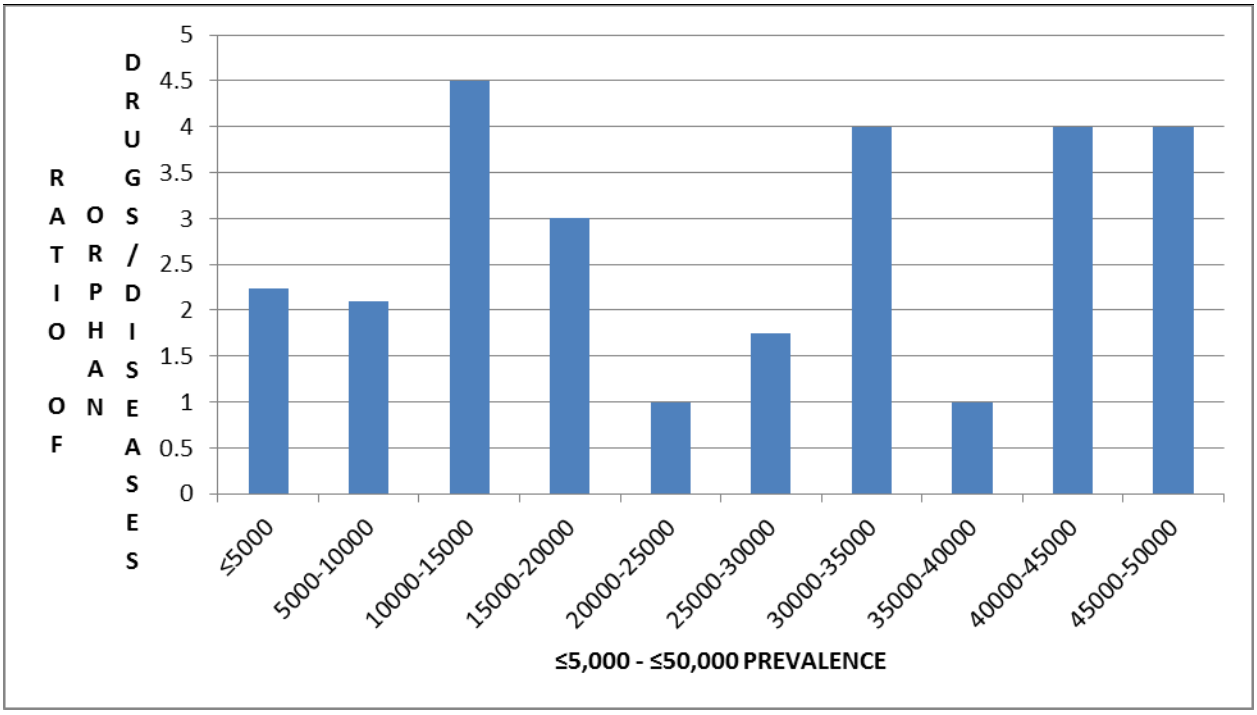

Figure 3: Ratio of Approved Drugs to Disease Incidence Groups. The graph depicts the ratio of the approved number of orphan drugs to the number of rare diseases in each prevalence group as listed in Table 1.

Discussion

This study demonstrated no correlation between the average number of drug approvals and the prevalence population. Although the hypothesis was that the disease with the lowest prevalence would have the most drugs approved, the primary analysis of data collected from the FDA website and NORD database did not support this hypothesis. According to Figure 1, which shows the number of drugs approved compared to the prevalence of the disease, it seems that the rarer the disease, the more likely an orphan drug was approved for that indication. The highest number of orphan drug approvals were found in the ≤ 5,000 and the 5,000-10,000 prevalence groups; 56 orphan drugs were approved for diseases with a population ≤ 5,000 and 21 orphan drugs were approved for diseases with prevalence between 5,000 and 10,000. However, Figure 2 demonstrates that the highest number of rare diseases were in the lowest prevalence groups; 25 diseases had a prevalence ≤ 5,000 and 10 diseases had a prevalence of 5,000-10,000. The rest of the prevalence groups from 10,000 to 50,000 had 4 or less diseases per an increment of prevalence.

Considering Figure 1 and 2 together, it is unclear if the ≤5,000 prevalence group has a higher likelihood of receiving priority in the drug approval process compared to a higher prevalence group. It is difficult to determine the factors that influence orphan drug approval for the rarest population because of the irregularity of data shown by Figures 1 and 2. For example, in Figure 1, the results demonstrated that it did not matter if the prevalence of the disease was lower or higher, because the number of approved drugs did not correlate to the prevalence rate of a disease. Additionally, according to Figure 3, there was no clear trend with prevalence in the ratio of the average number of approved orphan drugs per disease. Therefore, it was difficult to

determine if the prevalence rate of a disease impacts the number of approved orphan drugs per disease. Also, since there were limitations in confirming disease population rates for many unknown diseases or unlisted diseases on the NORD database, this research study requires further information to make final conclusions about the gathered data.

The primary limitations were that this study could not determine influencing factors other than the prevalence rate of a disease on development and approval of an orphan drug. Other factors that could have influenced orphan drug approval such as profit or sales data were also unavailable. Thus the current study tries to predict motivating factors by investigating disease prevalence. In addition, the information (such as incidence rate, prevalence rate or classification as a rare disease) was not available for several indications that were on the approved orphan drug list from the FDA web site. Therefore, these indications were excluded from this study in an effort to gather data from a dependable source. To assure consistency, data on disease populations were solely collected from the NORD database.

There are also limited scholarly publications on drug approval for the rarest diseases. This prevented data collection on the reasons behind their approvals and required reliance on a few published articles and approval notices from the FDA.

Surprisingly, there were multiple drugs approved per disease for each prevalence range in this study as shown in Figure 3. A brief investigation of the literature on randomly selected orphan drug approvals was conducted as to determine what might be supporting this study's results. Explanations may include multiple indications per orphan drug, severity of the diseases being treated, and government incentives. All of these could be a motivating factor for industry in the drug development process and for approval of orphan drugs for the rarest disease

indications. First, there are many orphan drugs approved for several indications and this may explain why there are multiple drugs per disease as shown in Figure 3. As an example, Parkinson's disease, which has a prevalence of 50,000, is treated with multiple drugs. An orphan drug approved for treating Parkinson's disease, Apomorphine hydrochloride, has also shown clinical significance in the improvement of movement irregularity in patients (US WorldMeds, 2015). Pharmaceutical companies are able to do more rigorous safety and efficacy clinical trials to determine the utility of an orphan drug for an indication with a higher prevalence population, like movement disorders. This fact could be a reason for why Figure 3 shows multiple orphan drugs approved per disease in all prevalence categories.

Another reason for multiple orphan drugs being approved for the rarest population is the severe impact of these rare diseases on people's lives. Lennox-Gastaut syndrome, a rare disease, has multiple orphan drugs approved possibly because of the incapacitating factors of the disease. A director in the FDA's Center for Drug Evaluation and Research, Dr. Russell Katz asserted regarding the approval of the orphan drug, Clobazam: "Lennox-Gastaut syndrome is a severe form of epilepsy that causes debilitating seizures, This is a difficult condition to treat, and it will be helpful to have an additional treatment option" ("FDA approves Onfi," 2014). This statement possibly relates to why there are more drugs available for the Lennox-Gastaut syndrome because of its severity. Furthermore, the impact on the early childhood age group of diseases such as Precocious Puberty and Respiratory Distress Syndrome may be an influencing factor for the pharmaceutical companies in developing orphan drugs. Treatments for respiratory failure in infants can reduce mortality and morbidity considerably according to Engle (2008). Likewise, the use of an orphan drug (Leuprolide acetate) decreases the symptoms of Precocious puberty, a

growth deficiency in early childhood which can cause psychological effects, delays in bone maturation, and late onset of pubertal changes (Carel, 2014). Improving health in vulnerable populations such as infants can be a major influence in developing orphan drugs for the betterment of future generations. Hence, developing multiple orphan drugs can be considered acts of goodwill by the pharmaceutical companies.

The pharmaceutical industry may also choose to develop orphan drugs due to the shorter clinical trials process, the more successful FDA approvals, and the ability to set higher prices for these drugs. Government incentives for rare disease drug development include a greater likelihood of receiving faster FDA approval by shorter requirements for clinical trials, the ability to demonstrate proof of concept and less competition between companies (Meekings, Williams & Arrowsmith, 2012, and Wellman-Labadie & Zhou, 2010). Orphan drug approvals were significantly higher in the year 2014 than previous years. There were 17 orphan drugs out of 41 novel drug approvals with a priority review of 100% for all 17 orphan drugs (Orphan Druganaut Blog, 2015). Additionally, an analysis performed by Meekings et al., (2012) of orphan drug value concluded that orphan drugs are an important portion of pharmaceutical sales and may actually allow the company to gain more profit than non-orphan drugs. For example, one of the drugs included in this analysis, eculizumab, had the highest price of any drug globally in 2010 at a cost of US $409,500 per year. It is indicated for the treatment of paroxysymal nocturnal hemoglobinuria, which has a small patient population, but led to $541 million in sales in just the year 2010 (Meekings et al., 2012). Lately, personalized medicine which emphasizes developing drugs targeted to more specific subsets within a larger disease population is becoming more

popular. This approach, even while benefiting a smaller patient population, may still be profitable because companies can charge higher prices for these drugs.

In addition to the stimulating factors presented above, further research is needed to fully understand the motives of pharmaceutical companies to develop orphan drugs for the rarest diseases. Some of the questions a future researcher might consider are:

Does the amount of money spent on research and drug development for rare disease prevent pharmaceutical companies from investing in these drugs?

Is the cost of developing orphan drugs for the rarest populations higher than for non-orphan drugs?

How much profit is gained by pharmaceutical companies from sales of orphan drugs?

Does the cost of orphan drug development have implications for the many patients facing these rare diseases?

Conclusion

Overall, this study supports that the Orphan Drug Act promotes drug development for rare diseases. There is no clear trend in prevalence versus drug approvals or the number of drugs per disease. However, there were multiple drugs approved per disease for every prevalence group. There were 3 motivation factors influencing pharmaceutical companies which were discussed in this paper: multiple indications for the same drug, goodwill towards populations with severe disease, government incentives toward orphan drug development. In addition, there are more questions to be investigated on what influences pharmaceutical companies in developing orphan drugs for the rarest disease population. Understanding this could allow the government to further promote orphan drug development and thus benefit these populations facing severe diseases.

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Appendix A

Rare Diseases from the Orphan Drug List Included in this Study

The following table shows the 96 rare diseases with a prevalence of less than 200,000 patients.

Disease Name
Acne Rosacea
Acquired hemophilia
Acromegaly
Acute Intermittent Porphyria
AIDS
Amyotrophic Lateral Sclerosis
Angioedema
Anthrax
Antithrombin Deficiency
Apnea of prematurity
Atypical hemolytic uremic syndrome
Barrett Esophagus
Botulism
Carnitine Deficiency Syndrome
Castleman's disease
Cervical Dystonia
Chronic Granulomatous Disease
Chronic inflammatory demyelinating polyneuropathy
Chronic lymphocytic leukemia
Chronic Myelogenous Leukemia
Crohn's Disease
Cryptococcosis
Cushing Syndrome
Cutaneous T-Cell Lymphomas
Cystic Fibrosis
Cystinosis
Cystinuria
Cytomegalovirus Infection
Dupuytren's disease

Fabry's disease
Familial hypercholesterolemia
Familial Mediterranean fever
Gastrointestinal stromal tumors
Gaucher Disease
Glanzmann's thrombasthenia
Growth Hormone Deficiency
Growth hormone insensitivity syndrome
Hairy Cell Leukemia
Hemophilia A
Hemophilia B
Hepatic encephalopathy
Hepatitis B
Hodgkin's lymphoma & non-hodgkin lymphoma
Homocystinuria
Hunter Syndrome (Mucopolysaccharidosis Type II)
Huntington's Disease
Hypoparathyroidism
Idiopathic pulmonary fibrosis
Juvenile Rheumatoid Arthritis
Lennox-Gastaut Syndrome
Lepromatous leprosy
Malaria
Malignant hyperthermia syndrome
Mantle cell lymphoma
Mastocytosis
Mesothelioma
Mucopolysaccharidosis (MPS) Type IV A (Morquio A syndrome)
Mucopolysaccharidosis Type I
Multiple Myeloma
Multiple Sclerosis
Mycosis fungoides
Myelodysplastic syndromes
N-acetylglutamate synthetase deficiency
Narcolepsy
Noonan syndrome
Ornithine Transcarbamylase Deficiency
Orthostatic Hypotension
Osteopetrosis

Paget's Disease
Parkinson's Disease
Paroxysmal nocturnal hemoglobinuria
Peyronie's disease
Pheochromocytoma
Pompe Disease
Precocious Puberty
Primary Biliary Cirrhosis
Pulmonary Arterial Hypertension
Respiratory Distress Syndrome, Infant
Short bowel syndrome
Sickle Cell anemia
Sjogren's syndrome
Smallpox
Thrombotic Thrombocytopenic Purpura
Thyroid Cancer
Toxoplasmosis
Transverse Myelitis
Treatment of mucopolysaccharidosis Type VI (Maroteaux-Lamy syndrome)
Tuberculosis
Turner's Syndrome
Tyrosinemia type 1
Ulcerative Colitis
Vernal Keratonconjunctivitis
Von Willebrand Disease
Wegener's Granulomatosis
Wilson's disease
Zollinger-Ellison syndrome

Appendix B

Orphan Drug Approvals for Diseases with a Prevalence Rate ≤50,000

The following table shows the 53 rare diseases with a prevalence of less than 50,000 which were analyzed in this study.

Name of Disease	**Names of Orphan Drugs accounted**	**prevalence population ≤50,000**	**Amount of Orphan Drugs**
Acromegaly	Octreotide, Pegvisomant, Lanreotide	19,100	3
Amyotrophic Lateral Sclerosis	Riluzole	30,000	1
Antithrombin Deficiency	Antithrombin III (human), recombinant human antithrombin	4,000	2
Atypical hemolytic uremic syndrome	Eculizumab	300	1
Carnitine Deficiency Syndrome	Levocarnitine	900	1
Castleman's disease	Siltuximab	30,000	1
Chronic inflammatory demyelinating polyneuropathy	Immune Globulin (Human)	19,100	1
Chronic Myelogenous Leukemia	Interferon alfa-2a,Busulfan, Imatinib, Dasatinib, nilotinib, bosutinib, omacetaxine mepesuccinate	4,000	7
Cushing Syndrome	Corticorelin ovine triflutate,mifepristone, pasireotide	4,100	3
Cutaneous T-Cell Lymphomas	Denileukin diftitox, Bexarotene, Vorinostat, pralatrexate, romidepsin, Belinostat	300	6
Cystic Fibrosis	Dornase alfa, Tobramycin for inhalation, aztreonam, ivacaftor	30,000	4
Cystinosis	Cysteamine, Cysteamine hydrochloride, cysteamine enteric coated	2,400	3
Cystinuria	Tiopronin	38,500	1
Fabry's disease	Ceramide trihexosidase/alpha-galactosidase A	3,900	1
Gastrointestinal stromal tumors	Imatinib mesylate, regorafenib	8,900	2

Gaucher Disease	Alglucerase injection, miglustat, velaglucerase-alfa, Taliglucerase alfa, Imiglucerase, eliglustat	6,000	6
Hairy Cell Leukemia	Pentostatin for injection, Cladribine	6,000	2
Hemophilia A	Desmopressin acetate, Coagulation factor VIIa (recombinant), anti-inhibitor coagulant complex, antihemophilic factor (recombinant), porcine sequence	31,200	4
Hemophilia B	Coagulation Factor IX (human), Coagulation factor IX (recombinant), Fc fusion protein	6,200	3
Homocystinuria	Betaine	1,000	1
Hunter Syndrome (Mucopolysaccharidosis Type II)	Idursulfase	1,600	1
Huntington's Disease	Tetrabenazine	30,000	1
Idiopathic pulmonary fibrosis	nintedanib, Pirfenidone	7,750	2
Juvenile Rheumatoid Arthritis	Etanercept,meloxicam, adalimumab, canakinumab	44,400	4
Lennox-Gastaut Syndrome	Felbamate, Lamotrigine, Topiramate, rufinamide, clobazam	46,000	5
Lepromatous leprosy	Clofazimine, Thalidomide	175	2
Malaria	Mefloquine HCL, Quinine sulfate,	1,200	2
Malignant hyperthermia syndrome	Dantrolene sodium suspension for injection	1,300	1
Mesothelioma	pemetrexed disodium	300	1
Mucopolysaccharidosis Type I	Laronidase	3,200	1
Multiple Myeloma	Melphalan, Bortezomib, lenalidomide, doxorubicin HCL liposome injection, plerixafor, carfilzomib,pomalidomide	12,700	7
Mycosis fungoides	Meclorethamine	300	1
Myelodysplastic syndromes	azacitidine, decitabine	10,650	2
N-acetylglutamate synthetase deficiency	carglumic acid	6,300	1
Narcolepsy	Modafinil, Oxybate	2,350	2
Ornithine Transcarbamylase Deficiency	Benzoate and phenylacetate, sodium phenylbutyrate	2,550	2
Osteopetrosis	Interferon gamma-1b	1,250	1

Parkinson's Disease	Selegiline HCl, Apomorphine HCl	50,000	2
Paroxysmal nocturnal hemoglobinuria	Eculizumab	325	1
Pompe Disease	Recombinant human acid alpha-glucosidase; alglucosidase alfa	8,000	1
Precocious Puberty	Histrelin acetate, Nafarelin acetate, Leuprolide acetate,	45,950	3
Primary Biliary Cirrhosis	Ursodiol	1,525	1
Pulmonary Arterial Hypertension	Epoprostenol, Bosentan, Treprostinil, Iloprost inhalation solution, ambrisentan, tadalafil, treprostinil (inhalational), macitentan,riociguat	450	9
Respiratory Distress Syndrome, Infant	Colfosceril palmitate, cetyl alcohol, tyloxapol,Beractant, Pulmonary surfactant replacement, porcine	50,000	6
Thrombotic Thrombocytopenic Purpura	Rho (D) immune globulin intravenous (human),immunoglobulin intravenous (IVIG), eltrombopag, romiplostim	1,300	4
Thyroid Cancer	Thyrotropin alpha, Vandetanib, cabozantinib, Sorafenib	43,000	4
Toxoplasmosis	Sulfadiazine	8,350	1
Transverse Myelitis	Baclofen	1,400	1
Treatment of mucopolysaccharidosis Type VI (Maroteaux-Lamy syndrome)	N-acetylgalactosamine-4-sulfatase, recombinant human	3,750	1
Tuberculosis	Rifampin, isoniazid, pyrazinamide, Aminosalicylic acid, Rifapentine	17,000	5
Von Willebrand Disease	Human plasma coagulation Factor VIII, Antihemophilic factor (human)	21,150	1
Wegener's Granulomatosis	Rituximab	8,450	1
Wilson's disease	Trientine HCl, Zinc acetate	9,275	2